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33 CASES OF MULTIPLE MYELOMA WITH MASSIVE BONE DESTRUCTION: REPORT OF A 10-YEAR STUDY IN NORTHEASTERN IRAN

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ABSTRACT

The author studied 133, 856 admissions over a ten-year period and found 138 cases of primary tumors of bone. Of these only 33 were multiple myeloma. Incidence, clinical manifestation, age, sex and etiology are reported, and the effect of four different chemotherapy regimens are evaluated.
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INTRODUCTION

Multiple myeloma, a malignant proliferation of antibody-secreting plasma cells, is characterized by high blood levels of monoclonal immunoglobulin, usually IgG. There are billions of myeloma cells, but generally they each secrete the saune Ig, indicating that the disease is clonal. Usually the blood lymphocyte count is not increased, but the saune Ig found free in the serum is detected on the surfaces of a subset of circulating B cells and their precursors indicating that multiple myeloma reflects proliferation of a clone of lymphoid cells which ultimately differentiates into Ig-secreting plasma cells. For many years multiple myeloma was considered a rare malignant disorder for which only palliative treatment was available. During the past ten years considerable progress has been made in the treatment of patients with this disease. Multiple myeloma is the most common bone marrow malignancy in Iran. The incidence of the disease in recent years has increased. A ten-year study of 133,856 admissions in our institution revealed 138 primary tumors of bone, but histologic type revealed 33 cases of a hematopoietic tumor that was multiple myeloma.

The goal of this paper is to compare the incidence, clinical manifestation of the disease, age, sex, and serum parameters, as well as to report the effect of four different chemotherapy regimens which were evaluated in 33 patients with multiple myeloma.

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MATERIALS AND METHODS

This report is an analysis of 33 consecutive cases of multiple myeloma treated at Ghaem Medical Center between September 1978 and April 1988. The diagnosis was based on bone marrow plasmacytosis exceeding 10% and a myeloma globulin peak on serum and Bence-Jones protein in urine with severe lytic bone lesions. Depression of normal serum immunoglobulins was also present.

RESULTS

Treatment regiments

Between September 1978 and October 1982, 13 patients were assigned at random to one of three different combinations of melphalan and cyclophosphamide and prednisone (MCP). As indicated in Table I, 20 patients were treated with melphalan-cyclophosphamide-vincristine-prednisone (MCVP). Between November 1983 and April 1988, this regimen was carried out at three-week intervals. All patients received treatments in doses adjusted to produce bone marrow toxicity (eg, a nadir in granulocytes between 1,000 and 2,500/mm^3).

Evaluation of response

Response was evaluated no sooner than four weeks after the start of therapy. The effect of treatment could

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TABLE I
Frequency of Response From Different Drug Combinations

	No. Treated	Response Rate	% All
M+C+P	13	40	40
Melphalan, 6 mg/m^2 / day / 4			
Cyclophosphamide, 500 mg/m^2/IV day 1			
Prednisone 60 mg / m^2 / day, 4 q 4 weeks			
M+C+V+P	20	60	60
Vincristine, 1 mg IV day 1			
Melphalan 5 mg / m^2, PO / day x 4			
Cyclophosphamide, 100 mg / m^2 PO day x 4			
Prednisone 60 mg / m^2, PO day x 4 q 3 weeks			

TABLE II
Comparability of Patient Groups

	MCP	MCVP
No. Patients	13	20
Age -- years (Median)	54	60
Sex (% Male)	60	56
Race (% White)	100	100
Pretreatment Abnormalities (% of Total)		
Hemoglobin < 8.5 gm%	22	18
Calcium > 11.5 mg/100ml	1	0
BUN > 40 mg/100ml	5	4
Tumor Mass Grade		
% High	40	36
% Intermediate	30	24
% Low	30	40

not be evaluated in patients who died during the first four weeks; these patients were considered to have had early deaths (we excluded four such cases from our study.) Clinical response was based on criteria previously presented in detail. These criteria[1] required that both of the following be sustained for at least two months: (1) a decrease in the production rate of serum myeloma protein to less than 25% of the pretreatment value, and (2) disappearance of Bence - Jones protein excretion, calculation of the serum protein production rate required, considerations of the serum concentrations of myeloma globulins, the plasma and volume, and the catabolic rate of the myeloma globulin as affected by the serum concentration.[2]

Previous studies had demonstrated that changes in tumor mass were underestimated when calculations did not consider the changing catabolic rate of IgG globulins and changing plasma volume.[3]

Comparing treatment groups

The frequency and severity of specific disease complications were evaluated in each group of patients receiving the different induction or maintenance treatment evaluated in this study (Table II). The absolute tumor mass before the start of chemotherapy was defined in each patient from clinical criteria described in former articles.

DISCUSSION

Myeloma is a diffuse neoplasm which originates from a single cell within the bone marrow. The abnormal clone of plasma cells proliferates and creates a mechanical burden which disables the skeletal system in the physiologic state. Marrow, tissue and trabeculae of bone share the limited space within the vertebrae, pelvis, ribs and proximal portions of the long bones.[5] The population of myeloma cells, by virtue of their considerable mass, displace and erode internal bony architecture.

According to the new study, tumor kinetics have provided a guide to the relationship between cell mass and the clinico-radiologic manifestation of the disorders.[6] Patients are first apt to develop symptoms when the total tumor population reaches 0.2 to 1.0 x 10^{12} cells. The loss of volume of hematopoietic tissue results in anemia. At this point, diffuse bone demineralization is apparent in skeletal roentgenograms. The tumor is generally, but not invariabley, evenly distributed throughout the bone marrow, and needle aspiration usually reveals that plasma cells comprise more than 15% of the nucleated cells.

The myeloma cell may be morphologically indistinguishable from a normal plasma cell, but frequently, immaturity, pleomorphism, and invasive mitotic activity are evident.[7] The plasma cells which constitute the escaped clone responsible for myeloma retain capacity to synthesize polypeptides. Each clone has a signature, a specific light chain, or intact immunoglobulin molecule which accummulates in the serum. Sixty percent of patients with myeloma have a monoclonal IgG spike in the serum.

The next most common abnormality is an IgA spike which occurs in more than 20% of cases. IgD myeloma occurs in 1% to 2% of cases, while monoclonal production of IgE and IgM are rare. In our studies, both changes were IgG, IgA, and occasionally pure light chain uria. In our series the change is consistent, with 62% IgG, 34% IjA and only 4% light chain uria were reported.

In this study no patient had non-producing myeloma protein. Nor did anyone have plasma cell leukemia during the study or in the follow-up period. At diagnosis the myeloma staging was made and most cases were at stage A. Clinical presentation of these 33 patients is summarized in Table III. The clinical features of multiple myeloma have been reviewed elsewhere.[8]

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TABLE III
Features At Diagnosis In 33 Patients With Multiple Myeloma

Manifestation	Percent	Comments
Age (years)	22-52	
Sex	(Male, female) 3:1	
Race	All white	
Fever	3%	Only with infection
Bacterial infection	More than 30%	Only pulmonary
Amyloidosis	Less than 10%	Only kidney involved
Proteinuria	Bence Jones 50%	
Azotemia	Less than 25%	In terminal phase
Skeletal Osteolytic Lesions	More than 70%	Disseminated
Osteoporosis	Common, more than 90%	
Neurologic	Root pain, cord 5%	Paralysis
Bone pain	95%	
Serum protein: IgG	62%	
IgA	34%	
IgM	0	
Light chain uria	4%	
Bleeding diathesis	20% of cases	
Serum osmolarity	None	
Hemoglobin < 12 gm/100ml	67%	
Calcium > 10 mg100ml	2%	
Creatinine > 2 mg/100ml	10%	
Plasma cell in bone marrow (median%)	100%	

Skeletal involvement

Conventional roentgenograms showed skeletal abnormalities in 78% of our patients with multiple myeloma. According to a study by Durie, et al,[9] a close relationship was demonstrated between the osteoclast activating factor (OAF) production by bone marrow cells and the extent of skeletal lesions.

The characteristic lesions in multiple myeloma are punched-out lytic areas without associated osteoblastic reaction. Roentgenography is the most sensitive and reliable method for demonstration of skeletal involvement in multiple myeloma. The common sites of skeletal involvement in our cases are those bones principally involved in hematopoietic function: spine, pelvis, skull, ribs, and femoral and humeral shafts.

In our cases, the disease was multicentric and consisted of a lytic lesion. Plasmacytoma (solitary lesion) was never seen, nor have we ever seen secondary calcification due to hypercalcemia in the lungs and kidneys.

CONCLUSION

For many years multiple myeloma was considered a rare malignant disorder for which only palliative treatment was avaliable. A large fraction of patients were incapacitated to varying degrees from pathologic fractures, anemia and recurrent infection, and the median survival time from diagnosis was less than one year. During the past years considerable progress has been made in the treatment of patients with this disease. More frequent and earlier diagnosis, along with improved management of specific disease complications, were among the many important advances which have been reviewed.[10] No series of patients with multiple myeloma surviving for more than ten years has been reported.[11] Long-term survival among patients with multiple myeloma is uncommon unless this group includes patients presenting with a solitary plasmacytoma that eventually progresses; patients with smoldering low cell mass or osteosclerotic myeloma; patients with monoclonal gammapathy of undetermined significance and patients with idiopathic Bence-Jones proteinuria that evolves to symptomatic multiple myeloma. A few patients survived for ten years or longer.[12] The incidence of such survival was estimated at 2.2%. In our series except for two patients, all had eight years.[13] Renal insufficiency and hypercalcemia were more common in the large series, so those two are major prognostic factors.[13] Other findings such as the degree of anemia, size and type of monoclonal protein in serum, the presence of bone lytic lesions and the percentage of bone marrow plasma cells help differentiate the long term survivors from others. At the present time the method of treatment of multiple myeloma has changed and the method of allogeneic bone marrow transplantation with the use of HLA-matched sibling donors appears to be a promising method of treatment of patients with multiple myeloma.[14]

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